Growth Hormone Treatment and Left Ventricular Dimensions in Turner Syndrome

Lea Ann Matura, PhD, Vandana Sachdev, MD, Vladimir K. Bakalov, MD, Douglas R. Rosing, MD, and Carolyn A. Bondy, MD

Objective To determine whether cardiac dimensions were different in girls with Turner syndrome (TS) who received growth hormone (GH) compared with those who did not receive GH.

Study design This retrospective, cross-sectional study analyzed echocardiograms in 86 females with TS divided into GH-treated (n = 67) and untreated (n = 19) groups. The subjects all participated in the National Institutes of Health protocol between 2001 and 2006.

Results The average age was 16.2 years (range, 10 to 25 years), and average duration of GH treatment was 4.4 years (range, 1 to 14 years). The GH-treated group was taller by ~7 cm ($P = .004$), but cardiac dimensions normalized to body surface area (BSA), including septal and posterior wall thickness and left ventricular (LV) mass and internal diameters, did not differ significantly between the 2 groups. The fractional shortening index was similar in the 2 groups. Multiple regression analyses indicated that BSA, but not duration of GH treatment, predicted LV dimensions in girls with TS.

Conclusions GH treatment of girls with TS increases stature but does not disproportionately affect cardiac dimensions. *(J Pediatr 2007;150:587-91)*

Turner syndrome (TS; 45,X) is the most common chromosomal disorder in females, occurring in ~1/2500 live female births.[1] Short stature and ovarian failure are the most prevalent findings, but the most medically significant feature is congenital heart disease with a high risk for aortic dilatation and dissection.[2-4] Along with anatomic defects, recent studies have found electrocardiographic abnormalities and evidence of autonomic and diastolic dysfunction in individuals with TS, suggesting a more extensive involvement of the cardiovascular system than was previously appreciated.[5-8]

Although girls with short stature in the context of TS are not usually growth hormone (GH)-deficient, the US Food and Drug Administration has approved treatment with recombinant human GH to augment adult height.[9-12] Girls with TS are typically treated with GH for ~5 years using higher pharmacologic doses than normally used in GH-deficient states.

GH actually promotes generalized somatic growth and has significant direct and indirect effects on the cardiovascular system.[13] GH excess resulting from tumors produces an increased heart rate and cardiac output in early stages, followed by cardiac hypertrophy and eventually cardiomyopathy.[13] Aortic and mitral regurgitation and arrhythmias are also more prevalent in individuals with acromegaly. GH treatment of GH-deficient individuals increases cardiac mass and output.[14,15] Treatment of normal volunteers with GH doses similar to those used to treat TS (0.06 mg/kg/day) increases cardiac output and left ventricular mass (LVM) in just 4 weeks.[16] Finally, treatment of GH-deficient children with exogenous GH has been associated with disproportionate left ventricular (LV) growth.[17,18]

See editorial, p 572

From the Developmental Endocrinology Branch, National Institute of Child Health and Human Development (L.A.M., V.K.B., C.A.B.) and National Heart, Lung and Blood Institute (V.S., D.R.R.), National Institutes of Health, Bethesda, MD.

Supported by the intramural research program of the National Institute of Child Health and Human Development, National Institutes of Health.

The authors have nothing to disclose and have no potential conflict of interest, real or perceived, to report. Lea Ann Matura wrote the first draft of the manuscript. No one involved in the production of the manuscript received any honorarium, grant, or other form of payment.

Submitted for publication Oct 18, 2006; last revision received Dec 6, 2006; accepted Feb 1, 2007.

Reprint requests: Dr. Lea Ann Matura, National Institutes of Health, CRC 1-3330, 10 Center Drive, Bethesda, MD 20892. E-mail: maturale@mail.nih.gov.

0022-3476/$ - see front matter

10.1016/j.jpeds.2007.02.009

BSA	Body surface area	LVIDD	Left ventricular internal diastolic dimension
GH	Growth hormone	LVM	Left ventricular mass
IVS	Interventricular septal thickness	PW	Posterior wall thickness
LV	Left ventricular	TS	Turner syndrome

The cardiac involvement in TS has sparked concern over potential adverse cardiovascular effects of GH treatment. Two echocardiography studies reported "normal" LV morphology and function in GH-treated girls with TS[19,20]; however, these studies included no GH-untreated girls with TS for comparison. In the present retrospective study, we examined cardiac variables using echocardiography in girls with TS who received GH treatment and compared them with a group who were not treated.

METHODS

Study Subjects

Study subjects were part of the TS natural history protocol, which was approved by the National Institute of Child Health Institutional Review Board. All adult participants and parents of minor children gave written informed consent, and minors gave informed assent. The TS protocol includes studies of bone mineral density, metabolic function, and cardiovascular imaging. Study subjects were recruited mainly through notices on the National Institutes of Health website (http://turners.nichd.nih.gov/). Inclusion criteria were phenotypic females older than age 6 years who had a 50-cell peripheral karyotype in >70% of cells, demonstrating loss or partial loss of the second sex chromosome.

Consecutive participants between age 10 and 25 and parents of minors were asked about GH use. GH treatment had been received by 67 subjects and not received by 21 subjects. The usual daily dose was 0.05 mg/kg/day. Each subject's height and weight were measured by National Institutes of Health Clinical Research Center nurses using a SR model SR555 scale (SR Instruments, Tonawanda, NY) with a height rod. Body mass index (BMI) and body surface area (BSA) were calculated using the DuBois and DuBois formulas.

Echocardiography

Transthoracic 2-dimensional and Doppler echocardiography were performed on all subjects using commercially available echocardiography machines. Standard parasternal, apical, and subcostal views were obtained with the participants in the left lateral recumbent position. The images were stored digitally and on VHS videotape for analysis. Cardiac measurements were performed according to American Society of Echocardiography guidelines.[21] LVM was calculated using the following anatomically validated formula:

$$LVM\,(\mathrm{g}) = 0.8\,(1.04\,[IVS + PW + LVIDD]^3 - [LVIDD]^3) + 0.6,$$

where IVS is interventricular septal thickness, PW is posterior wall thickness, and LVIDD is left ventricular internal diastolic dimension.[22] LVM was divided by BSA (m^2) to adjust for the effect of body size.[23]

Statistical Analysis

Data are presented as mean ± standard deviation. Group means were compared by analysis of variance, with age and body size variables as covariates as indicated by the Fisher's probable least squares difference test. Multiple linear regression was used to analyze the effects of GH on cardiac dimensions. Analyses were performed using Stat View for Windows, version 5.0.1 (SAS Institute Inc, Cary, NC).

RESULTS

Study Subjects

The study group included 86 subjects age 10 to 25 years with reliable information on GH use. Of these, 19 had never used GH and 67 (78%) had used GH for 1 year or longer. The most common reason for not using GH was late diagnosis, followed by satisfaction with the patient's height. The average duration of GH use was 4.4 years (range, 1 to 14 years). Twenty-three subjects were still taking GH at the time of echocardiography for this study. Of the 67 subjects receiving GH treatment, 1 had hypertension, 16 (24%) had a bicuspid aortic valve, and 2 had a history of coarctation of the aorta. Of the 19 subjects not treated with GH, 1 had hypertension, 3 (16%) had a bicuspid aortic valve, and none had coarctation. None of the subjects had significant aortic or mitral regurgitation. The 2 groups were similar in age and body mass, but the GH-treated group was significantly taller (Table I).

Effect of GH on Cardiac Dimensions

The effect of GH status on cardiac dimensions is also reported in Table I. All of the measures were within the normal age group range. To adjust for body size differences, cardiac dimensions were normalized to BSA. There were no significant differences in any cardiac measures between the GH-treated and untreated groups (Table I). Fractional shortening, a measure of LV function, was also similar in the 2 groups. In addition, measures of diastolic function, E/A ratio (peak flow velocity in early diastole [E wave] vs that at atrial contraction [A wave]) and mitral deceleration time, were normal and not significantly different between the groups.

We further investigated whether the duration of GH treatment affects cardiac dimensions. We used multiple regression analyses to evaluate the duration of GH treatment along with age and BSA as covariates (Table II). These analyses indicated that the number of years receiving GH did not independently influence cardiac growth. We also performed this analysis on the group currently receiving GH (n = 23) and obtained similar results (data not shown).

DISCUSSION

This study investigated the effects of GH treatment lasting an average of 4 to 5 years on cardiac dimensions in

Table I. Somatic and cardiac dimensions in GH-treated versus untreated patients with TS

	No GH (n = 19)		Treated with GH (n = 67)		
	Mean (SD)	Range	Mean (SD)	Range	*P* value
Age (years)	16.5 (4.8)	10 to 25	16.1 (4.3)	10 to 25	.727
Height (cm)	138.6 (11.2)	115.0 to 157.1	145.7 (9.4)	122.0 to 162.7	.004
Weight (kg)	47.4 (16.4)	25.8 to 96.4	50.1 (13.8)	24.2 to 84.9	.309
BMI (kg/m^2)	24.2 (5.7)	15.6 to 39.1	23.3 (4.9)	15.4 to 39.4	.855
BSA (m^2)	1.3 (0.2)	1.0 to 2.0	1.4 (0.2)	0.9 to 1.9	.070
Septum/BSA (mm/m^2)	5.4 (0.9)	4.1 to 6.3	5.2 (0.8)	3.7 to 7.4	.367
PW/BSA (mm/m^2)	5.4 (0.9)	4.1 to 6.3	5.1 (0.7)	3.5 to 6.6	.057
LVIDD diastole/BSA (mm/m^2)	30.5 (4.4)	22.0 to 39.8	30.5 (4.4)	22.4 to 41.3	.970
LVIDD systole/BSA (mm/m^2)	19.2 (2.2)	15.4 to 22.5	19.1 (3.4)	12.0 to 27.9	.948
LVM/BSA (g/m^2)	59.1 (16.2)	39.3 to 108.8	63.4 (12.5)	40.6 to 90.7	.224
Fractional shortening (%)	36.1 (8.1)	27.0 to 50.0	37.6 (6.1)	25.0 to 53.7	.422
E/A ratio	1.8 (0.6)	1.0 to 3.2	1.7 (0.5)	1.1 to 3.4	.319
DT	125.1 (36.3)	80.7 to 208.0	140.8 (68.0)	63.6 to 451.0	.409

DT, Mitral deceleration time.
E/A ratio is the peak flow velocity in early diastole (E wave) versus that at atrial contraction (A wave). Mean values are compared by analysis of variance, with age as a covariate, followed by Fisher's probable least squares difference test. Cardiac measurements are normalized to BSA. Fractional shortening = (LVIDD − IVS)/LVIDD.

Table II. Effect of GH treatment on septum, PW, LVIDD disastole, LVIDD systole, and LVM, controlling for age, years receiving GH therapy, and BSA

Cardiac dimension	Estimate	SE	*t* ratio	*P* value
Septum				
$R^2 = 0.246$, $P = .0004$, n = 67				
Intercept	3.604	0.814	4.430	<.0001
Age	0.013	0.039	0.335	.739
Years on GH	0.002	0.043	0.042	.966
BSA	2.363	0.800	2.952	.004
PW				
$R^2 = 0.409$, $P = <.0001$, n = 67				
Intercept	2.643	0.679	3.892	.0002
Age	−0.003	0.033	−0.092	.927
Years on GH	−0.005	0.036	−0.138	.891
BSA	3.172	0.668	4.748	<.0001
LVID diastole				
$R^2 = 0.222$, $P = .001$, n = 67				
Intercept	29.230	3.147	9.288	<.0001
Age	0.045	0.151	0.300	.765
Years on GH	0.032	0.166	0.193	.848
BSA	8.422	3.096	2.720	.008
LVID systole				
$R^2 = 0.116$, $P = .050$, n = 67				
Intercept	20.344	2.817	7.223	<.0001
Age	0.022	0.135	0.162	.872
Years on GH	0.232	0.149	1.559	.124
BSA	3.140	2.771	1.133	.261
LVM				
$R^2 = 0.017$, $P = .778$, n = 67				
Intercept	80.418	20.737	3.878	.0003
Age	−0.954	0.996	−0.958	.342
Years on GH	−0.401	1.094	−0.367	.715
BSA	14.317	20.399	0.702	.485

girls and young women with TS, using echocardiography to compare LV wall thickness and diameters in the 2 groups. As expected, the GH-treated group was significantly taller and had correspondingly greater cardiac dimensions compared with age-matched untreated subjects. Adjusting for the GH-treated groups' larger body size, no significant differences in

cardiac dimensions were found between the 2 groups. Fractional shortening, an index of LV function, was also similar in the 2 groups. These findings demonstrate that cardiac size in GH-treated girls with TS is proportionate to their greater body size, suggesting that GH treatment, even in pharmacologic doses, does not produce abnormal cardiac growth or hypertrophy in girls with TS.

An earlier study investigated, also by echocardiography, the effects of 3 GH doses given over 7 years in Dutch girls with TS.[20] Although this study included no untreated control group, cardiac dimensions in the girls with TS were within the normal range, and no apparent GH dose effect was seen in the 3 different dosage groups. Another study compared cardiac measures in GH-treated girls with TS versus age- and size-matched eukaryotic girls.[19] No differences in LVM and LV volume were found, but mild diastolic dysfunction was seen in the subjects with TS; however, this finding likely can be attributed to significant differences in heart rate and blood pressure between the 2 groups. It is well established that on average, girls with TS have a higher heart rate and blood pressure than age-matched controls.[24]

Although it is advantageous to have an untreated group with TS for comparison, a major drawback of our study is that the groups were not randomly assigned. Thus, selection bias could be contributing to the findings. For example, if girls with cardiac involvement were selectively excluded from GH treatment by their caregivers, then the comparison might not be valid. However, the frequency of cardiovascular defects was similar in the 2 groups; for example, the prevalence of a bicuspid aortic valve was about 20% in both groups. Also, it was abundantly clear that the major reason for nontreatment was late diagnosis due to suboptimal medical care, because the untreated girls were very short and generally as severely affected as the treated group. Finally, it is possible that adverse cardiovascular effects may not be apparent until more time has passed, and thus more long-term follow-up is necessary to confirm the finding of no harmful effects of GH treatment on the cardiovascular system of patients with TS.

Our study establishes that pharmacologic GH treatment has little effect on LV size in patients with TS, at least over an intermediate (4 to 5 years) period of observation. Thus we confirm the findings of earlier studies that lacked control groups with TS and extend the results of our own previous study showing no apparent effect of GH on aortic diameter in TS.[25]

Curiously, there seems to be no cardioselective effect of GH in girls with TS, although GH treatment of GH-deficient children has been associated with disproportionate LV growth.[17,18] Perhaps this is because GH deficiency is associated with relative cardiac hypoplasia and associated catch-up growth with GH treatment. In any case, the present findings reinforce that girls with TS are not especially vulnerable to GH-induced cardiac hypertrophy.

The authors would like to acknowledge Marilyn St. Peter, RDCS, for technical assistance with the echo data.

REFERENCES

1. Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 1991;87:81-3.

2. Lin AE, Lippe BM, Geffner ME, Gomes A, Lois JF, Barton CW, et al. Aortic dilation, dissection, and rupture in patients with Turner syndrome. J Pediatr 1986; 109:820-6.

3. Sybert VP. Cardiovascular malformations and complications in Turner syndrome. Pediatrics 1998;101:e11.

4. Bondy C. New issues in the diagnosis and management of Turner syndrome. Rev Endocr Metab Disord 2005;6:269-80.

5. Bondy CA, Van PL, Bakalov VK, Sachdev V, Malone CA, Ho VB, et al. Prolongation of the cardiac QTc interval in Turner syndrome. Medicine (Baltimore) 2006;85:75-81.

6. Bondy CA, Ceniceros I, Van PL, Bakalov VK, Rosing DR. Prolonged rate-corrected QT interval and other electrocardiogram abnormalities in girls with Turner syndrome. Pediatrics 2006;118:e1220-5.

7. Gravholt CH, Hansen KW, Erlandsen M, Ebbehoj E, Christiansen JS. Nocturnal hypertension and impaired sympathovagal tone in Turner syndrome. J Hypertens 2006;24:353-60.

8. Andersen NH, Hjerrild BE, Sorensen K, Pedersen EM, Stochholm K, Gormsen LC, et al. Subclinical left ventricular dysfunction in normotensive women with Turner's syndrome. Heart 2006;92:1516-7.

9. Soriano-Guillen L, Coste J, Ecosse E, Leger J, Tauber M, Cabrol S, et al. Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. J Clin Endocrinol Metab 2005; -0470.

10. Pasquino AM, Pucarelli I, Segni M, Tarani L, Calcaterra V, Larizza D. Adult height in sixty girls with Turner syndrome treated with growth hormone matched with an untreated group. J Endocrinol Invest 2005;28:350-6.

11. The Canadian Growth Hormone Advisory Committee. Impact of growth hormone supplementation on adult height in Turner syndrome: results of the Canadian randomized controlled trial. J Clin Endocrinol Metab 2005;90: 3360-6.

12. van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, et al. Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low-dose estrogens. J Clin Endocrinol Metab 2003;88:1119-25.

13. Colao A, Vitale G, Pivonello R, Ciccarelli A, Di Somma C, Lombardi G. The heart: an end-organ of GH action. Eur J Endocrinol 2004;151:S93-101.

14. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. Circulation 2003;108:2648-52.

15. Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, et al. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 2002;109:1345-50.

16. Cittadini A, Berggren A, Longobardi S, Ehrnborg C, Napoli R, Rosen T, et al. Supraphysiological doses of GH induce rapid changes in cardiac morphology and function. J Clin Endocrinol Metab 2002;87:1654-9.

17. Shulman DI, Root AW, Diamond FB, Bercu BB, Martinez R, Boucek RJ Jr. Effects of one year of recombinant human growth hormone (GH) therapy on cardiac mass and function in children with classical GH deficiency. J Clin Endocrinol Metab 2003;88:4095-9.

18. Radetti G, Crepaz R, Paganini C, Gentili L, Pitscheider W. Medium-term cardiovascular effects of high-dose growth hormone treatment in growth hormone-deficient children. Horm Res 1999;52:247-52.

19. Radetti G, Crepaz R, Milanesi O, Paganini C, Cesaro A, Rigon F, et al. Cardiac performance in Turner's syndrome patients on growth hormone therapy. Horm Res 2001;55:240-4.

20. Sas TC, Cromme-Dijkhuis AH, de Muinck Keizer-Schrama SM, Stijnen T, van Teunenbroek A, Drop SL. The effects of long-term growth hormone treatment on cardiac left ventricular dimensions and blood pressure in girls with Turner's syndrome. Dutch Working Group on Growth Hormone. J Pediatr 1999;135:470-6.

21. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards,

Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.
22. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-8.
23. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992;20:1251-60.
24. Nathwani NC, Unwin R, Brook CG, Hindmarsh PC. Blood pressure and Turner syndrome. Clin Endocrinol (Oxf) 2000;52:363-70.
25. Bondy CA, Van PL, Bakalov VK, Ho VB. Growth hormone treatment and aortic dimensions in Turner syndrome. J Clin Endocrinol Metab 2006;91:1785-8.

50 Years Ago in *The Journal of Pediatrics*

Editorial: Are there too many people in the world?

J Pediatr 1957;50:655-6

In 1957, the editors of *The Journal of Pediatrics* marveled at the astonishing growth of the world's population, having increased from 1,810 million in 1920 to 2,652 million: "Thus in the last twenty-five years the world population has increased roughly 50 per cent." The editors expressed concern that population growth (estimated to be 1.5% per year) was far outstripping food growth (estimated at 1% per year), observing that "[i]t is stated that half of the people in the world today are hungry." The editors did not view population control as a realistic solution to the inadequate food supply, describing it as "wish thought."

In fact, in the 50 intervening years since these observations, world population growth has declined somewhat (currently estimated at 1.14%), although the world's population has more than doubled to 6,400 million persons.[1] However, global food production has increased dramatically; it is estimated that world agriculture produces 17% more calories per capita in 2006 than it did 30 years ago, despite the increase in the world's population of nearly 100% in that same time interval. Globally, it is estimated that there is a sufficient amount of food to provide the world's entire population with 2,720 kilocalories per day.[2] It is anticipated that the number of underweight children will decline from 163.8 million in 1990 to 113.4 million in 2015, a change of −31% (95% CI, −40% to −20%). In developed countries, the number was estimated to decline from 1.2 to 0.6 million, a change of −54% (95% CI, −94% to 244).[3]

But as a result of poverty, disease, and war, the good news is not evenly distributed. In Africa, it is anticipated that the number of underweight children will increase from 25.8 million in 1990 to 43.3 million in 2015, a change of 68% (95% CI, 63%-74%). Sub-Saharan, Eastern, Middle, and Western Africa are all expected to experience substantial increases in the number of underweight children (77%, 102%, 72%, and 54%, respectively).[3] Further, not well appreciated half a century ago, micronutrient disorders affect a large proportion of the world's population (including deficiencies in iron (estimated 2 billion people), iodine (estimated 740 million people), and vitamin A (estimated 100 to 140 million children).[2] Finally, not contemplated a half century ago, in the past decade a global epidemic of obesity has emerged in both developed and developing countries.[4]

Bonita Stanton, MD
Professor and Schotanus Family Endowed Chair of Pediatrics
Pediatrician-in-Chief
Carman and Ann Adams Department of Pediatrics
Children's Hospital of Michigan
Wayne State University School of Medicine
Detroit, Michigan
10.1016/j.jpeds.2006.11.018

REFERENCES

1. United Nations Statistics Division. Population and Vital Statistics Report: Series A. http://unstats.un.org/unsd/demographic/products/vitstats/seriesa2.htm. Accessed September 25, 2006.
2. World Hunger Education Series. World Hunger Facts 2006. http://unstats.un.org/unsd/demographic/products/vitstats/seriesa2.htm Accessed September 25, 2006.
3. de Onis M, Blossner M, Borghi E, Frongillo EA, Morris R. Estimates of global prevalence of childhood underweight in 1990 and 2015. JAMA 2004;291:2600-6.
4. Popkin BM. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. Am J Clin Nutr 2006;84:289-98.